(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 347 890 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: **89111321.9**

(51) Int. Cl.[4]: **A23L 1/305**

(22) Date of filing: **21.06.89**

A request for correction of the word "transfusion" into "infusion","59-16187"into "591687 and "compositional"into "composition"has been filed pursuant to Rule 88 EPC. A decision on the request will be taken during the proceedings before the Examining Division (Guidelines for Examination in the EPO, A-V, 2.2).

Amended claims in accordance with Rule 86 (2) EPC.

(30) Priority: **22.06.88 JP 155744/88**
26.08.88 JP 212758/88
25.10.88 JP 270558/88
28.10.88 JP 273826/88
07.12.88 JP 310772/88

(43) Date of publication of application:
27.12.89 Bulletin 89/52

(84) Designated Contracting States:
DE FR IT

(71) Applicant: **MORISHITA PHARMACEUTICAL CO., LTD.**
3-8, Dosho-machi 3-chome Chuo-ku
Osaka-shi Osaka-fu(JP)

Applicant: **AJINOMOTO CO., INC.**
5-8, Kyobashi 1-chome, Chuo-ku
Tokyo 104(JP)

(72) Inventor: **Ozeki, Kohji**
3-22 Kojogaoka Minakuchi-cho Koga-gun
Shiga-ken(JP)
Inventor: **Tsukamoto, Yoshitsugu**
715 Kawanami Gokasho-cho Kanzaki-gun
Shiga-ken(JP)
Inventor: **Yaginuma, Hideya**
2030-89 Mikumo Kosei-cho Koga-gun
Shiga-ken(JP)
Inventor: **Sato, Makoto**
166-40 Harimada-cho
Moriyama-shi Shiga-ken(JP)

(74) Representative: **Strehl, Schübel-Hopf, Groening, Schulz**
Maximilianstrasse 54 Postfach 22 14 55
D-8000 München 22(DE)

(54) Amino acid nutrient compositions.

(57) This invention provides stabilized and/or dense L-amino acid nutrient compositions, i.e., amino acid transfusion solutions, which contain at least one oligopeptide having at least one residue of L-Tryptophan, L-Tyrosine, L-Leucine, L-Isoleucine and L-Valine.

EP 0 347 890 A1

AMINO ACID NUTRIENT COMPOSITIONS

Field of the Invention:

The present invention provides stabilized and/or dense L-amino acid nutrient compositions. Such stabilized and/or concentrated L-amino acid nutrient compositions may be prepared by using oligopeptides whose molecules contain at least one L-amino acid residue of some specific L-amino acids.

Discussion of the Background:

When patients in spite of necessity cannot orally take in, or can take in orally only an insufficient amount of amino acids or proteins, in various diseases or in preoperative or postoperative stage, etc, L-amino acid nutrient compositions whose main ingredients are L-amino acids, e.g., L-amino acid transfusion solutions for intravenous administration (referred to hereinafter as "amino acid transfusion solutions") have been widely utilized for the purpose of nutrient supplementation.

In general, however, with the passage of time, amino acid transfusion solutions tend to form degradation products and discolor yellow. Therefore, to prevent discoloration, hitherto stabilizers have been used, such as inorganic salts of sulfurous acid or pyrosulfurous acid, e.g. sodium hydrogensulfite, potassium hydrogensulfite, sodium sulfite, potassium sulfite, sodium pyrosulfite, potassium pyrosulfite, etc. A method for stabilization using sulfurous acid salts of basic amino acids is also disclosed (Japanese Patent Application Laid-Open No. 49-102831). These hydrogensulfites or sulfites are very effective for preventing coloration of amino acid transfusion solutions. Among them, hydrogensulfites are superior.

However, it is known that the hydrogensulfites and sulfites react with amino acids. They are very reactive, in particular, with cystine, methionine or tryptophan. For example, these salts react with cystine to cleave the disulfide bond and give cysteine thiosulfate. Furthermore, the salts react with methionine in the presence of oxygen to form methionine sulfoxide. The salts cause an extremely complicated reaction with tryptophan and the major reaction products are highly reactive formylkynurenine, 2,3-dioxyindolealanine, etc. As such, these salts are effective for apparent prevention of coloration of amino acid transfusion solutions but give reaction products which are harmful to the living body. Moreover, the hydrogensulfites or sulfites react with protein to cleave disulfide bonds or bind to protein itself when they are taken into the living body. Furthermore, the salts also react with nucleic acid bases or other compounds in the living body and are known to have a potent mutagenecity.

Accordingly, it is not preferred to use the hydrogensulfites or sulfites as stabilizers for amino acid transfusion solutions. However, no stabilizers better than these salts are known so that the prior art cannot help using the salts in a trace amount under the actual situation.

It has been now found that the prime cause of instability such as coloration, etc. of amino acid transfusion solutions is attributable to L-tryptophan Trp) and the coloration is proportional to the concentration of Trp in amino acid transfusion solutions.Trp is one of the essential amino acids. It is known that Trp greatly affects protein synthesis in liver and it has been a demand to increase the Trp concentration in an amino acid transfusion solution. As already stated, however, there have been serious problems in preparation of amino acid transfusion solutions that an increase in the Trp concentration results in increased coloration and the like.

A first problem to be solved by the present invention is, under the above-described prior art, to provide stable, L-amino acid-containing nutrient aqueous compositions which contain the Trp ingredient in a desirable amount but no stabilizers such as hydrogensulfites or sulfites conventionally used.

On the other hand, recently, since researches on the amino acid metabolism under the sick conditions have been promoted and hence the roles of the various amino acids under the sick conditions have been made clear, the stream of the development of the amino acid transfusion solutions is divided into two directions, that is, the development of amino acid transfusion solutions according to the respective sick conditions taking the therapeutic aspect into consideration on one hand and the development of general-purpose amino acid transfusion solutions for correcting the nutrient characteristics relatively common to the various sick conditions on the other hand.

Among L-amino acids used for amino acid transfusion solutions, L-tyrosine (Tyr) has been proven essential for liver diseases, uremia, immature infants, newborns, etc. Inter alia, with uremia patients, especially Tyr indicates a low level. This is due to that the activity of L-phenylalanine (Phe) hydroxylase is low and thus that the production of Tyr from Phe is inadequate. The decrease in the protein synthesis due

to the Tyr deficiency has been recognized to extremely lower the nutrient conditions of the patient. Further, since Tyr is a precursor to catecholamine, it is also indicated that if this is inadequate, various neurosis signs are brought about, and with these patients, Tyr has been gradually taking the position as an essential amino acid. For that reason, it is the present situation that an amino acid transfusion solution in which Tyr is formulated so as to adapt to these sick conditions has been sought. However, the solubility of Tyr in water is merely 0.045 g/dl at 25°C, and it is difficult to freely formulate a necessary amount thereof as an ingredient for transfusion solution.

As regards the formulation of Tyr in transfusion solutions, compositions based on nutrient formulations for healthy humans have heretofore been used, for example, those based on amino acid compositions of human milk or the whole egg according to the report of FAO special committee, 1957. etc. However, as described earlier, in the body of healthy humans Tyr can be synthesized in an adequate amount from Phe, but such synthesis is impossible with certain sick conditions and thus Tyr is considered as an essential amino acid. Therefore, it is evident that the nutrient formulation for these patients is different from the nutrient formulation for healthy humans.

The formulation for sick conditions taking this into consideration is disclosed in Japanese Patent Application Laid-Open No. 59-16187, where it is indicated that favorable results are obtained when Tyr is contained in the range of 1/12 - 1/17 based on Phe and at a concentration of 0.45 - 0.55 g/l. However, according to the research on the metabolism of the ingested essential amino acid Phe in vivo, it has been discovered that 50 - 70 % of the ingested Phe has been converted into Tyr. It is thought that Phe must be present at a concentration of 5.0 - 10.0 g/l in an ordinary amino acid transfusion solution. Even by simple calculation considering the conversion rate described above, it may be presumed that the part 2.5 -7.0 g/l of Phe in the formulation must be replaced by Tyr under sick conditions. When this is taken into consideration, the formulation presented in Japanese Patent Application Laid-Open No. 59-16187 has been designed in the range of Tyr solubility, and it seems uncertain that the sick conditions are well considered. On the other hand, no amino acid transfusion solutions containing such a high concentration of Tyr have been known.

In the meantime, several methods for increasing the concentration of Tyr have been proposed. Japanese Patent Application Laid-Open No. 56-8312 discloses a method which utilizes peptides such as L-alanyl-L-tyrosine, L-arginyl-L-tyrosine, L-tyrosyl-L-arginine etc., Japanese Patent Application Laid-Open No. 61-247354 discloses glycyl-L-tyrosine and L-alanyl-L-tyrosine and Japanese Patent Application Laid-Open No.62-151156 discloses L-aspartyl-L-tyrosine. However, with respect to any of these known preparations it seems uncertain that the necessary formulation of Tyr has been fully studied.

A second problem to be solved by the present invention is, under the above-described prior art, to provide an amino acid nutrient transfusion composition of a new formulation which contains sparingly soluble tyrosine in an amount necessary at a ratio achieving the purpose without being subject to the pharmaceutical restrictions and also can exert an excellent nutrient effect to the various intended diseases.

As has been discussed earlier, recently, studies on amino acid metabolism under morbid conditions have been advanced, and have revealed the roles of various amino acids under pathological conditions. As a result of these studies the trend of developing amino acid transfusion solutions has gone into two different directions: one is to pursue amino acid transfusion solutions used in respective diseases laying a stress on therapy and the other is to pursue all-purpose amino acid transfusion solutions with an attempt to correct nutritious imbalance relatively common to various morbid conditions.

With respect to the branched chain L-amino acids (BCAA) L-leucine (Leu), L-isoleucine (Ile) and L-valine (Val) among L-amino acids used in amino acid. transfusion solutions, their sitological significance has been clarified over wide areas including application to surgical seizures, hepatic insufficiency, renal insufficiency, septicemia, premature infant, etc. For development of transfusion solutions in either direction described above, attention has been drawn to these amino acids as one of the most important amino acid group. It is known that unlike other amino acids, the branched chain L-amino acids are metabolized mainly in tissues other than liver, and, in particular, Leu has an activity to accelerate synthesis of muscular protein and prevent its decomposition. It is also known that when the branched chain amino acids have been administered to humans in relatively large quantities, their blood concentration does not increase very much and an influence on amino acid distribution in blood is small. Such findings have increased a demand for highly concentrated amino acid transfusion solutions for administration via the central vein in which the ratio of the branched chain amino acids to the total L-amino acids (BCAA/TAA) is increased.

However, solubilities of Leu, Ile and Val in water at 25°C are 2.19, 4.12 and 8.85 g/dl, respectively. When other amino acids are co-present, any of the solubilities decreases. For example, a mixture of Leu and Ile in almost equimolar amounts has a solubility of approximately 2.2 g/dl and a mixture of Leu, Ile, Val, L-methionine (Met) and Phe has a solubility of approximately 4.5 g/dl. Thus, when it is wished to raise a concentration of the branchd chain amino acids, a concentration of other L-amino acids should be extremely

reduced so that unbalanced distribution of L-amino acids in blood is caused. Accordingly, its application has been limited to special cases for patients with hepatic encephalosis, etc. That is, it has been difficult to prepare highly cocentrated amino acid transfusion solutions containing other L-amino acids in a well-balanced state to be suited for any desired purpose, while increasing a ratio of the branched chain amino acids to the total L-amino acids.

Some proposals have already been made to increase the concentration of the L-amino acid content using water soluble oligopeptides, though the proposals don't pay attention particularly to the branched chain amino acids. For example, in Japanese Patent Application Laid-Open No. 56-140923, there is disclosed a method using at least two oligopeptides containing a glycine residue as the N-terminal. According to this method, however, the proportion of the specific amino acid, glycine (Gly), becomes extremely high to cause imblanced distribution of L-amino acids in blood, which is not preferable. Furthermore, in Japanese Patent Application Laid-Open No. 61-247354, there is disclosed a method using oligopeptide(s) containing a glycine residue as the N-terminal in combination with oligopeptide(s) containing as the N-terminal a residue from at least one amino acid selected from the group consisting of Ala, L-arginine (Arg) and L-lysine (Lys). However, as is demonstrated in the Laid-Open Applications, an increased concentration of the branched chain amino acids is accompanied by a high concentration of Gly, Ala, Arg or Lys. As a result, it is difficult to provide sitologically preferred compositions.

The present invention aims at providing highly dense amino acid transfusion solutions which can exhibit excellent nutrient effect in various diseases. That is, a third problem to be solved by the present invention is, under the above-described prior art, to provide L-amino acid compositions for transfusion in which the ratio of the branched chain amino acid components is increased, other amino acids are formulated to be present in a well balanced state and a high concentration can be achieved without any limitation on preparations.

Furthermore, as has been discussed above, as recent studies on amino acid metabolism under morbid conditions have been advanced, it has been desired to develop amino acid transfusion solutions used for pathologic conditions such as surgical seizures, hepatic insufficiency, renal disorder, septicemia, premature infant, etc. In particular, attention has been drawn to the branched chain L-amino acids (BCAA) metabolized in organs other than liver and by enhancing the proportion of BCAA to the total L-amino acids (TAA), nutrient effects have been increased in pre-operative and post-operative stages. For treatment of some specific disease, there is known Fischer et al's composition applicable to patients with hepatic encephalosis in which the BCAA content is increased while the contents of Met, Phe and Trp are restricted; or the like.

The ratio of BCAA to be incorporated has also been studied, and, as a result, it has been found that an increased ratio of Leu is necessary for exhibiting good effects on sitological parameters. These studies further revealed that when the ratio of BCAA to TAA (BCAA/TAA) is 25 to 60%, good results are obtained. In addition, as has been stated above, even though BCAA is intravenously administered in a relatively large dose, its blood concentration does not increase so that imbalanced distribution of L-amino acids in blood does not occur. Based on these research results, it has been demanded to increase the ratio of BCAA to TAA (BCAA/TAA) and increase the concentration of BCAA more. In particular, as the complete intravenous administration utilizing the central veins has been advanced, the amount of water administered is limited so that a much higher concentration of a transfusion solution has been demanded, as has been also stated above. However, solubilities ot Leu, Ile and Val in water at 25°C are 2.19, 4.12 and 8.85 g/dl, respectively. When these amino acids are further mixed with other amino acids, any of the solubilities decreases, as has been already stated. Among them, it is difficult to increase the concentration of Leu, which is sitologically desirable. I.e., there has been a bar against the preparation of dense transfusion solutions having a high concentration of BCAA in compliance with the purpose of use.

Several proposals have already been made, as has been stated above, to increase the concentration of the L-amino acid components in general (Japanese Patent Application Laid-Open No. 56-140923 and Japanese Patent Application Laid-Open No. 61-247354). However, as is demonstrated in the Laid-Open Applications, an increased concentration of BCAA is accompanied by an increased concentration of other L-amino acids, and this is not preferred.

As a result of extensive investigations, the present inventors have found that by mixing a composition mainly composed of BCAA with an ordinary amino acid transfusion solution in a suitable ratio, an amino acid transfusion solution suited for various specific morbid conditions can be readily obtained.

A fourth problem to be solved by the present invention, with respect to the above-described prior art, is to provide BCAA compositions which are used for preparing amino acid transfusion solutions which are free from any preparation restrictions but contain BCAA in a large ratio suited for the purpose in a necessary dose by simply adding such BCAA composition to an ordinary amino acid transfusion solution when administered.

SUMMARY OF THE INVENTION

The present invention completed to solve the above problems relates, in one of its aspects, to stabilized and/or dense L-amino acid nutrient compositions in which at least one of some specific L-amino acids is contained partly or substantially completely in the form of oligopeptide(s) containing at least one residue of the same L-amino acid(s).

In a second aspect, the present invention relates to stabilizer-free nutrient transfusion compositions and more particularly, to stabilized, amino acid-containing nutrient transfusion compositions which are free of any stabilizer conventionally considered to be necessary.

In a third aspect, the present invention relates to a nutrient transfusion composition, and more specifically to an amino acid nutrient transfusion composition containing a dipeptide of L-tyrosine.

In a fourth aspect, the present invention relates to nutrient transfusion compositions, and more particularly to amino acid nutrient transfusion compositions which contain a dipeptide of Leu which is a branched chain amino acid.

In a fifth aspect, the present invention relates to novel compositions for amino acid transfusion solutions, and more particularly to compositions for amino acid transfusion solutions which compositions contain a dipeptide of branched chain L-amino acid(s).

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

A First Embodiment:

There are known among common transfusion solutions which are administered intravenously, glucose solutions, xylitol solutions, electrolyte solutions, lactic acid-added Ringer solutions and L-amino acid solutions.

Many various compositions have been proposed for amino acid transfusion solutions, but there still remain problems to be solved, as has been discussed above.

The present inventors have found, as a result of their profound research to solve such problems, that it is a solution common to the problems to use some specific L-amino acids in the form of their oligopeptides, and completed the present invention on the basis of these findings.

I.e., the present invention provides, in a first embodiment, amino acid transfusion solutions and mixtures of L-amino acids which form an amino acid transfusion solution when dissolved in water, in which solutions or mixtures at least one of Trp, Tyr, Leu, Ile and Val is partly or substantially completely in the form of oligopeptide(s).

Examples of such oligopeptides and their preparation will be mentioned later.

Amino acid transfusion solutions and mixtures of L-amino acids which give an amino acid transfusion solution when dissolved in water may be prepared in any conventional ways of preparing amino acid transfusion solutions and mixtures of L-amino acids which give an amino acid transfusion solution when dissolved in water, except that at least one of the above-mentioned specific amino acids is partly or substantially completely in the form of oligopeptide(s).

A Second Embodiment:

In view of the foregoing findings about the prime cause of the instability of amino acid transfusion solutions, the present inventors have made various investigations and have found that by using Trp in the form of dipeptide or tripeptide, instability of amino acid transfusion solutions such as discoloration, etc. can be prevented and at the same time, a high concentration of Trp can be achieved.

That is, the present invention provides, in a second embodiment, nutrient transfusion compositions containing essential L-amino acids characterized by containing Trp in the form of dipeptide or tripeptide containing at least one L-tryptophan residue and being free of any stabilizer.

It is to be noted that substantially all the Trp must be in the form of dipeptide or tripeptide in nutrient transfusion compositions of the present invention in order to realize the object.

Examples of the dipeptides and tripeptides used in the present invention include

L-tryptophyl-glycine (Trp-Gly), L-tryptophyl-L-alanine (Trp-Ala), L-tryptophyl-L-leucine (Trp-Leu), L-tryptophyl-L-isoleucine (Trp-Ile), L-tryptophyl-L-valine (Trp-Val), L-alanyl-L-tryptophan (Ala-Trp), L-leucyl-L-

tryptophan (Leu-Trp), L-isoleucyl-L-tryptophan (Ile-Trp), L-valyl-L-tryptophan (Val-Trp), glycyl-L-tryptophyl-glycine (Gly-Trp-Gly), glycyl-L-tryptophyl-L-alanine (Gly-Trp-Ala), glycyl-L-tryptopyl-L-leucine (Gly-Trp-Leu), L-alanyl-L-tryptophyl-glycine (Ala-Trp-Gly), L-alanyl-L-tryptophyl-L-alanine (Ala-Trp-Ala), L-alanyl-L-tryptophyl-L-leucine (Ala-Trp-Leu). Among these peptides, Trp-Ala and Trp-Leu are the best two in stabilizing activity, as will be seen from the test examples given hereinafter.

The peptides can be prepared by conventional peptide synthesis.

The amino acid composition in the nutrient transfusion compositions of the present invention may be a new one suited for a desired purpose or may be any conventional one, supposing that the dipeptide or tripeptide used are converted to the component L-amino acids.

According to the present invention, L-amino acids and oligopeptides may be used either in the free form or in the pharmaceutically acceptable salt forms such as metal salts, e.g., with sodium and potassium, mineral acid addition salts, e.g, with hydrochloric and sulfuric acids, and organic acid addition salts, e.g., with acetic and lactic acids.

The nutrient transfusion compositions of the present invention may also contain nutrients other than amino acids, such as electrolytes, trace elements, etc.

They are not critical in their concentration, and can have concentrations of known amino acid transfusion solutions. Their pH can be the same as those of known amino acid transfusion solutions, and may usually be in the range of about 4 to about 8. Their pH adjusting agents can be the same ones for known amino acid transfusion solutions.

The present invention will be described in more detail by referring to the examples and the test examples below.

EXAMPLE 1

To the amino acid composition shown in Table 1 was added 1.7 g of Trp-Ala. The mixture was dissolved in distilled water for injection by heating to make the whole volume 0.99 liter. After adjusting its pH to about 6.5 with an aqueous acetic acid solution, the whole volume was made 1 liter. The solution was filtered through a membrane filter having a pore diameter of 0.45µm. The filtrate was filled in a 200 ml glass bottle. After replacing the air with nitrogen gas, the bottle was tight-sealed. A nutrient solution for intravenous administration was then prepared by steam sterilization.

The preparation contained 1.3 g/l of Trp and 7.1 g/l of Ala supposing that the dipeptide was converted to the component L-amino acids, i.e., Trp and Ala.

Table 1

Amino Acid Composition (g)					
Ile	9.1	Val	14.0	Glu	0.5
Leu	12.9	Arg	9.0	Pro	5.0
Lys	7.1	His	5.0	Ser	1.7
Met	4.4	Gly	7.0	Tyr	0.4
Phe	7.0	Ala	6.5		
Thr	7.5	Asp	1.0		

In the table, Thr, His, Glu, Asp, Pro and Ser represent L-Threonine, L-Histidine, L-Glutamic acid, L-Aspartic acid, L-Proline and L-Serine, respectively.

EXAMPLE 2

To the amino acid composition shown in Table 2 was added 3.4 g of Trp-Ala. Subsequently, the mixture was treated in a manner similar to Example 1 to give a transfusion solution.

When the dipeptide was calculated as Trp and Ala, the solution contained 2.5 g/l of Trp and 4.1 g/l of Ala.

Table 2

Amino Acid Composition (g)					
Ile	7.5	Val	7.5	Cys	0.25
Leu	10.0	Arg	2.0	Glu	0.25
Lys	5.0	His	2.5	Orn	1.5
Met	5.0	Gly	2.0	Pro	2.0
Phe	5.0	Ala	3.0	Ser	1.0
Thr	2.5	Asp	0.25	Tyr	0.5

In the table, Cys and Orn represent L-cystein and L-ornithine, respectively.

EXAMPLE 3

To the amino acid composition shown in Table 3 was added 6.7 g of Trp-Ala. Subsequently, the mixture was treated in a manner similar to Example 1 to give a transfusion solution.

When the dipeptide was calculated as Trp and Ala, the solution contained 5.0 g/l of Trp and 4.7 g/l of Ala.

Table 3

Amino acid Composition (g)					
Ile	9.1	Val	14.0	Glu	0.5
Leu	12.9	Arg	9.0	Pro	5.0
Lys	7.1	His	5.0	Ser	1.7
Met	4.4	Gly	5.1	Tyr	0.4
Phe	7.0	Ala	2.5		
Thr	7.5	Asp	1.0		

EXAMPLES 4 to 7

The amino acids and dipeptides shown in Table 4 were mixed as is indicated under each example, and the mixtures were treated in a manner similar to Example 1 to give transfusion solutions.

Table 4

Amino Acid Compositions (g)				
	Example No.			
	4	5	6	7
Ile	7.2	9.1	9.1	7.5
Leu	11.3	12.9	12.9	10.0
Lys	8.1	7.0	7.1	5.0
Met	11.3	4.4	4.4	5.0
Phe	11.3	7.0	7.0	5.0
Thr	5.2	5.0	7.5	2.5
Val	8.3	14.0	14.0	7.5
Arg	0	9.0	9.0	2.0
His	5.7	4.0	5.0	2.5
Gly	0	3.0	7.0	2.0
Ala	0	0	6.5	2.0
Asp	0	1.0	1.0	0.25
Cys	0	0	0.5	0.25
Glu	0	0.5	0.5	0.25
Pro	0	4.0	5.0	2.0
Ser	0	1.7	1.7	1.0
Tyr	0	0.4	0.4	0.5
Orn	0	0	0	0.5
Trp-Ala	3.6	20.1	0	0
Ala-Trp	0	0	1.7	3.4

TEST EXAMPLE 1

With respect to 0.5% aqueous solution of each of the representative dipeptides, tripeptides and Trp, transmittance after sterilization (105°C, 60 minutes) was measured. The results are shown in Table 5.

In addition, solubility in water was determined. The results are shown in Table 6.

It is noted that any of the peptides are extremely stable as compared to Trp and its solubility is improved.

Table 5

	Transmittance after Sterilization (T%, 430 nm)
Trp	90.7
Trp-Gly	98.5
Trp-Ala	99.3
Trp-Leu	99.2
Ala-Trp	98.1
Gly-Trp-Gly	99.2
Gly-Trp-Ala	99.1

Table 6

Solubility in Water (g/dl)	
Trp	1.14
Trp-Gly	3.29
Trp-Ala	5.20
Trp-Leu	3.50
Ala-Trp	5.00

TEST EXAMPLE 2

With respect to the transfusion solutions obtained in Examples 1 to 4 and Comparative Examples 1 to 8, transmittance before and after sterilization (105° C, 80 minutes) was measured, respectively. The results are shown in Tables 7 to 10.

Table 7

Transmittance (T%, 430 nm)			
	Before Sterilization	After Sterilization	Difference in Transmittance
Example 1	99.2	98.9	0.3
Comparative Example 1	99.3	97.5	1.8
Comparative Example 2	99.2	99.0	0.2

COMPARATIVE EXAMPLE 1

A transfusion solution was prepared by following Example 1 except that Trp and Ala were used instead of Trp-Ala.

COMPARATIVE EXAMPLE 2

A transfusion solution was prepared by following comparative Example 1 except that 0.5 g/l of sodium hydrogensulfite was additionally added.

Table 8

Transmittance (T%, 430 nm)			
	Before Sterilization	After Sterilization	Difference in Transmittance
Example 2	99.6	99.2	0.4
Comparative Example 3	99.7	98.3	1.6
Comparative Example 4	99.8	99.5	0.4

COMPARATIVE EXAMPLE 3

A transfusion solution was prepared by following Example 2 except that Trp and Ala were used instead of Trp-Ala.

COMPARATIVE EXAMPLE 4

A transfusion solution was prepared by following Comparative Example 3 except that 0.5 g/l of sodium hydrogensulfite was additionally added.

Table 9

Transmittance (T%, 430 nm)			
	Before Sterilization	After Sterilization	Difference in Transmittance
Example 3	98.9	98.5	0.4
Comparative Example 5	98.9	95.2	3.7
Comparative Example 6	98.9	98.5	0.4

COMPARATIVE EXAMPLE 5

A transfusion solution was prepared by following Example 3 except that Trp and Ala were used instead of Trp-Ala.

COMPARATIVE EXAMPLE 6

A transfusion solution was prepared by following Comparative Example 5 except that 0.5 g/l of sodium hydrogensulfite was additionally added.

Table 10

Transmittance (T%, 430 nm)			
	Before Sterilization	After Sterilization	Difference in Transmittance
Example 4	99.6	99.3	0.3
Comparative Example 7	99.7	98.4	1.3
Comparative Example 8	99.7	99.4	0.3

COMPARATIVE EXAMPLE 7

A transfusion solution was prepared by following Example 4 except that Trp and Ala were used instead of Trp-Ala.

COMPARATIVE EXAMPLE 8

A transfusion solution was prepared by following Comparative Example 7 except that 0.5 g/l of sodium hydrogensulfite was additionally added.

As described above, it is understood that the compositions of the present invention provide high stability equivalent to the compositions in which sodium hydrogensulfite was incorporated.

According to the present invention, as is evident from the foregoing examples and test examples, amino acid nutrient transfusion compositions which are sufficiently stable can be provided without using stabilizers such as hydrogensulfites or sulfites harmful to the body. Furthermore, the Trp component can be contained in higher concentrations if necessary and desired, and transfusion solutions having new formulations which are suited for various purposes can be provided.

The dipeptide and tripeptide used in accordance with the present invention are stable in an aqueous solution and are not colored even after sterilization by heating. Furthermore, solubility in water is also improved.

In fact, the amino acid nutrient transfusion compositions of the present invention containing Trp in the form of dipeptide or tripeptide is not colored without containing any stabilizer therein but is sufficiently stable from an aspect of medical preparations.

The dipeptide or tripeptide used in accordance with the present invention is effectively utilized in the living body.

A Third Embodiment:

The present inventors have been studying in order to solve the second problem and, as a result, have discovered that the solubility of Tyr which is a pharmaceutical problem may be solved by using a dipeptide of Tyr and that in order to further obtain the effect of Tyr, the concentration of Tyr in an amino acid transfusion solution has an optimum range and that the optimum range is related to the concentrations of the other L-amino acids incorporated at the same time, and have accomplished the present invention based on these findings.

As has been described before, Tyr has been found to be an essential amino acid for certain sick conditions, and the necessity of a high concentration has been urged for practical purposes. However, owing to the pharmaceutical problems, comprehensive studies on the correlation of Tyr with other L-amino acids and concentrations thereof have not yet been done, and thus formulations to realize its higher concentrations have not been yet determined. Tyr is synthesized from its precursor essential amino acid Phe, and Phe is the most correlated amino acid.

Based on such consideration, the present inventors had thought that there must be a particular correlation between the amounts of Tyr and Phe incorporated and the amounts of essential L-amino acids and non-essential L-amino acids incorporated, and have continued the study. As a result, they have discovered an amino acid composition ratio which may be used for morbid conditions such as liver diseases, uremia etc. as well as for immature infants, newborn infants etc., and have accomplished the present invention.

Accordingly, the present invention provides, in a third embodiment, an amino acid nutrient transfusion composition containing essential amino acids, non-essential L-amino acids and at least one dipeptide containing at least one L-tyrosine residue, which is characterized by that when said dipeptide is calculated as the respective component L-amino acids, at least the respective amino acids indicated in Table 11 are contained in the respective ranges indicated therein, that the weight ratio of Tyr to Phe (Tyr/Phe) is 0.1 or more and that the concentration of Tyr is 0.6 g/l or more.

Table 11

Amino Acid	Composition Range (g/100 g-Total Amino Acids)
Ile	5.0 - 20.0
Leu	5.0 - 20.0
Lys	3.0 - 15.0
Met	1.0 - 10.0
Phe	1.0 - 10.0
The	2.0 - 12.0
Trp	0.25 - 5.0
Val	5.0 - 20.0
Ala	2.0 - 15.0
Arg	2.0 - 15.0
Asp	0 - 4.0
Cys	0 - 2.0
Glu	0 - 8.0
His	0 - 10.0
Pro	0 - 10.0
Ser	0 - 8.0
Tyr	0.5 - 10.0
Gly	3.0 - 15.0
Orn	0 - 5.0
Tau	0 - 15.0

The statement "when said dipeptide is calculated as the respective component L-amino acids" means that "when the amount of said dipeptide is calculated as the amounts of the respective L-amino acids formed when fully hydrolyzed".

As dipeptides containing at least one L-tyrosine residue used in the present invention, there may be preferably used L-threonyl-L-tyrosine (Thr-Tyr), L-leucyl-L-tyrosine (Leu-Tyr), L-isoleucyl-L-tyrosine (Ile-Tyr), L-valyl-L-tyrosine (Val-Tyr), L-tyrosyl-glycine (Tyr-Gly), L-tyrosyl-L-alanine Tyr-Ala), L-tyrosyl-L-leucine (Tyr-Leu), L-tyrosyl-L-isoleucine (Tyr-Ile), L-tyrosyl-L-valine (Tyr-Val), L-tyrosyl-L-aspartic acid (Tyr-Asp), L-tyrosyl-L-lysine (Tyr-Lys), L-tyrosyl-L-threonine (Tyr-Thr), L-tyrosyl-L-glutamic acid (Tyr-Glu) and L-tyrosyl-L-glutamine (Tyr-Gln).

These peptides can be prepared by conventional peptide synthesis.

By incorporating at least one dipeptide containing at least one L-tyrosine residue, an amino acid nutrient transfusion composition containing Tyr at a high concentration is presented.

Further, the amino acids and dipeptides according to the present invention may be used not only as free acid forms but also as pharmaceutically acceptable salts, for example, metal salts such as sodium salts, potassium salts etc., mineral acid salts such as hydrochlorides, sulfates etc. or organic acid salts such as acetates, lactates etc. Further, the amino acids other than those made into the dipeptides may also be used as pharmaceutically acceptable N-acyl derivatives, ester derivatives or oligopeptides. Furthermore, when they are made into amino acid transfusion compositions, such composition may be produced in the conventional manner by using conventionally employed stabilizers, pH modifiers etc.

An effective dosage of the total amino acids of the present invention is 60 - 90 g/day for adults.

The present invention will be more specifically described by the examples and test examples given below.

EXAMPLE 8

8.6 g of Tyr-Ala was added to the amino acid composition set forth in Table 12, dissolved in injectable distilled water by heating, and then the total amount was adjusted to 0.99 ℓ. Thereafter, the pH was adjusted to 6.0 - 7.0 with an acetic acid solution or other organic acid solution (lactic acid, malic acid, citric acid etc.), and the total amount was adjusted to 1 liter. This aqueous solution was filtered through a membrane filter having a pore diameter of 0.45 µm, filled into a 200 ml glass vial, followed by nitrogen replacement and tight-sealing.

This was sterilized by steam at high pressure to prepare a transfusion solution for intravenous administration.

This preparation contained Ala and Tyr at 3.0 g/l and 6.2 g/l, respectively, if the dipeptide was calculated as the respective component L-amino acids,

Table 12

Amounts of Amino Acids Incorporated (g/l)					
Ile	9.0	Val	10.0	Pro	5.0
Leu	13.0	Ala	6.0	Ser	3.0
Lys	10.0	Arg	10.0	Gly	5.0
Met	2.5	Asp	2.0	Tau	3.5
Phe	3.0	Cys	1.0		
Thr	5.0	Glu	2.0		
Trp	2.5	His	5.0		

EXAMPLE 9

7.2 g of Leu-Tyr was added to the amino acid composition set forth in Table 13, and thereafter by procedures similar to those described in Example 8, a transfusion solution for intravenous administration was prepared.

This preparation contained Leu and Tyr at 3.2 g/l and 4.4 g/l, respectively, if the dipeptide was calculated as the respective component L-amino acids.

Table 13

Amounts of Amino acids Incorporated (g/l)					
Ile	8.5	Val	10.0	Pro	6.0
Leu	12.6	Ala	12.0	Ser	3.0
Lys	12.0	Arg	9.0	Gly	10.0
Met	7.5	Asp	2.0	Tau	7.5
Phe	3.0	Cys	1.0		
Thr	8.0	Glu	2.0		
Trp	2.5	His	5.0		

EXAMPLE 10

11.8 g of Val-Tyr was added to the amino acid composition set forth in Table 14, and thereafter by procedures similar to those described in Example 8, a transfusion solution for intravenous administration was prepared.

This preparation contained the Val and Tyr at 4.9 g/l and 7.6 g/l, respectively, if dipeptide was calculated as the respective component L-amino acids.

Table 14

Amounts of Amino Acids Incorporated (g/l)					
Ile	7.0	Val	2.1	Pro	4.6
Leu	14.0	Ala	8.3	Ser	2.1
Lys	6.9	Arg	9.0	Gly	10.5
Met	5.7	Asp	3.0		
Phe	3.0	Cys	1.0		
Thr	6.3	Glu	3.5		
Trp	1.1	His	6.0		

EXAMPLES 11 - 20

The amino acid compositions and peptides set forth in Tables 15 and 15a were formulated, and thereafter by procedures similar to those described in Example 8, transfusion solution for intravenous administration were prepared.

Table 15

Amounts of Amino Acids and Dipeptides Incorporated (g/l)					
Amino Acids and Dipeptides	Example No.				
	11	12	13	14	15
Ile	7.5	7.0	7.5	10.0	7.3
Leu	13.0	14.0	12.8	12.0	14.2
Lys	9.1	9.5	10.0	8.0	9.5
Met	4.4	3.9	2.5	2.5	2.0
Phe	4.2	3.0	2.0	3.0	3.0
Thr	7.5	5.7	5.0	5.0	6.2
Trp	1.3	2.0	2.5	2.5	2.0
Val	8.0	7.0	12.0	6.5	7.5
Ala	7.1	7.0	6.0	6.0	5.9
Arg	9.0	10.5	10.0	10.0	7.0
Asp	1.1	1.0	2.0	2.0	2.0
Cys	0	1.0	1.0	1.0	0.5
Glu	0.5	1.4	2.0	2.0	4.5
His	5.0	5.0	5.0	4.0	4.1
Pro	5.0	5.0	5.0	3.0	4.5
Ser	1.7	3.0	3.0	2.5	3.0
Gly	6.5	5.9	5.0	6.0	7.5
Orn	0	0	1.0	1.5	0
Tau	0	0	3.2	0	3.5
Leu-Tyr	0	0	7.2	0	0
Ile-Tyr	0	3.4	0	0	0
Val-Tyr	0	0	0	10.8	0
Tyr-Gly	1.7	0	0	0	0
Tyr-Ala	0	0	0	0	5.4
Tyr Amount	1.3	2.1	4.4	7.0	3.9
Amount of the other Amino Acid in the peptide	Gly 0.5	Ile 1.5	Leu 3.2	Val 4.5	Ala 1.9

Table 15a

Amounts of Amino Acids and Dipeptides Incorporated (g/l)					
Amino Acids and Dipeptides	Example No.				
	16	17	18	19	20
Ile	8.0	9.0	8.5	9.1	5.6
Leu	14.0	13.0	13.0	13.1	12.5
Lys	9.5	10.0	12.0	8.1	9.3
Met	3.9	2.5	7.5	4.4	3.5
Phe	4.0	5.1	1.7	4.5	3.3
Thr	6.7	8.0	10.8	8.5	6.5
Trp	2.0	2.5	2.2	1.3	1.3
Val	8.0	11.0	7.4	9.0	4.5
Ala	5.5	2.5	12.0	6.0	3.1
Arg	10.5	8.8	10.3	9.0	8.9
Asp	1.0	3.0	1.7	2.7	3.4
Cys	1.0	1.0	0	0	1.0
Glu	1.0	2.0	0.9	4.5	6.5
His	4.4	5.0	8.5	5.0	6.0
Pro	5.0	5.0	8.5	5.0	3.3
Ser	3.0	2.5	2.9	1.7	2.2
Gly	7.0	5.0	13.5	7.0	9.7
Orn	0	0	0	0	0
Tau	0	2.5	5.5	0	0
Leu-Tyr	0	0	0	1.0	0
Ile-Tyr	0	0	0	0	0
Val-Tyr	0	0	6.2	0	0
Tyr-Gly	1.5	0	0	0	0
Tyr-Ala	0	7.1	0	0	8.8
Tyr Amount	1.1	5.1	4.0	0.6	6.3
Amount of the other Amino Acid in the peptide	Gly 0.5	Ala 2.5	Val 2.6	Leu 0.5	Ala 3.1

TEST EXAMPLE 3

An SD strain male rat of a body weight of about 170 g was planted with a silicone rubber catheter in the right upper great vein under anesthetized condition, and immediately subjected to transfusion application by an intravenous hyperalimentation therapy for a week (total calorie: 332 Kcal/Kg/day, nitrogen: 1.83 gN/Kg/day). The three applied nutrient transfusion solutions had the same composition of sugars, electrolytes, vitamins and trace elements but different amino acid compositions. The transfusion solution tested was that of Example 8, and as comparison transfusion solutions, Transfusion Solutions I and II formulated as in Table 16 were used.

The study on the effects were conducted by examining the change in body weight and the nitrogen balance. As a result, it is observed that the transfusion solution of Example 8 gave a remarkable improvement as compared with the comparison transfusion solution as shown in Table 17.

Table 16

Amino Acid Compositions of Transfusion Solution I and II		
Amino Acids	Transfusion Solution I (g/l)	Transfusion Solution II (g/l)
Ile	9.0	9.0
Leu	13.0	13.0
Lys	10.0	10.0
Met	2.5	2.5
Phe	3.0	8.7
Thr	5.0	5.0
Trp	2.5	2.5
Val	10.0	10.0
Ala	9.0	9.0
Arg	10.0	10.0
Asp	2.0	2.0
Cys	1.0	1.0
Glu	2.0	2.0
His	5.0	2.0
Pro	5.0	5.0
Ser	3.0	5.0
Tyr	0.4	0.4
Gly	7.6	5.0
Tau	3.5	3.5

Table 17

Nutrient Effect of the Example 8 Transfusion Solution		
Amino Acid Transfusion Solution	Gain in Body Weight (g/7 days)	Nitrogen Balance (g/7 days)
Solution I	11.0	1.0
Solution II	22.1	1.5
Solution of Example 8	28.3	1.7

TEST EXAMPLES 4 - 7

Using the transfusion solutions of Examples 9, 10, 13 and 20 and the comparison transfusion solutions set forth in Table 18 and 18a, procedures similar to those in Test Example 3 were conducted. The results are shown in Table 19.

Table 18

Compositions of Comparison Transfusion Solutions				
	Test Example 4		Test Example 5	
Amino Acids and Dipeptides	Comparison Transfusion Solution for Example 9		Comparison Transfusion Solution for Example 10	
	III	IV	V	VI
Ile	8.5	8.5	7.0	7.0
Leu	15.8	15.8	14.0	14.0
Lys	12.0	12.0	6.9	6.9
Met	7.5	7.5	5.7	5.7
Phe	3.0	7.0	3.0	9.9
Thr	8.0	8.0	6.3	6.3
Trp	2.5	2.5	1.1	1.1
Val	10.0	10.0	7.0	7.0
Ala	12.0	12.0	8.3	8.3
Arg	9.0	9.0	9.0	9.0
Asp	2.0	2.0	3.0	3.0
Cys	1.0	1.0	1.0	1.0
Glu	2.0	2.0	3.5	3.5
His	5.0	5.0	6.0	6.0
Pro	6.0	6.0	4.6	4.6
Ser	3.0	3.0	2.1	2.1
Tyr	0.4	0.4	0.4	0.4
Gly	11.8	10.0	13.6	10.5
Orn	0	0	0	0
Tau	7.5	7.5	0	0

Table 18a

Compositions of Comparison Transfusion Solutions				
	Test Example 6		Test Example 7	
Amino Acids and Dipeptides	Comparison Transfusion Solution for Example 13		Comparison Transfusion Solution for Example 20	
	VII	VIII	IX	X
Ile	7.5	7.5	5.6	5.6
Leu	16.0	16.0	12.5	12.5
Lys	10.0	10.0	9.3	9.3
Met	2.5	2.5	3.5	3.5
Phe	2.0	6.0	3.3	9.0
Thr	5.0	5.0	6.5	6.5
Trp	2.5	2.5	1.3	1.3
Val	12.0	12.0	4.5	4.5
Ala	6.0	6.0	6.2	6.2
Arg	10.0	10.0	8.9	8.9
Asp	2.0	2.0	3.4	3.4
Cys	1.0	1.0	1.0	1.0
Glu	2.0	2.0	6.5	6.5
His	5.0	5.0	6.0	6.0
Pro	5.0	5.0	3.3	3.3
Ser	3.0	3.0	2.2	2.2
Tyr	0.4	0.4	0.4	0.4
Gly	7.4	5.0	12.3	9.7
Orn	1.0	1.0	0	0
Tau	3.2	3.2	0	0

Table 19

Nutrient Effects of the Examples 9 - 12 Transfusion Solution			
Test Example	Amino Acid Transfusion Solution	Gain in Body Weight (g/7 days)	Nitrogen Balance (g/7 days)
4	Transfusion Solution III	12.5	1.0
	Transfusion Solution IV	24.8	1.7
	Transfusion Solution of Example 9	29.3	2.0
5	Transfusion Solution V	15.9	1.5
	Transfusion Solution VI	27.3	1.8
	Transfusion Solution of Example 10	30.3	2.0
6	Transfusion Solution VII	13.8	1.3
	Transfusion Solution VIII	18.7	1.8
	Transfusion Solution of Example 13	23.4	1.8
7	Transfusion Solution IX	13.0	1.2
	Transfusion Solution X	23.3	1.6
	Transfusion Solution of Example 20	25.9	1.9

TEST EXAMPLE 8

Using an SD strain male rat of a body weight of about 170 g, the cortex part of one of the kidneys was surgically enucleated under anesthetized condition, and two weeks later, the other kidney was enucleated. Two weeks after the enucleation of the kidney, the urea nitrogen in blood and the creatinine level were measured, and that having concentrations of 60 mg/dl or higher and 1.4 mg/dl or higher, respectively, was taken as a model attacked by a kidney disease. This rat was planted with a silicone rubber catheter in the right upper great vein, and the transfusion maintenance was conducted by an intravenous hyperalimentation therapy for a week (total calorie: 319 Kcal/Kg/day, nitrogen: 0.982 gN/Kg/day). The applied nutrient transfusion solutions had the same composition of sugars, electrolytes, vitamins and trace elements but different amino acid compositions. The transfusion solution tested was that of Example 8 and Comparison Transfusion Solutions I and II shown in Table 16 were used for comparison.

As a rsult, as shown in Table 20, it was possible to confirm that the transfusion solution of Example 8 exerted a remarkable improvement in the change in weight and the nitrogen balance.

Table 20

Nutrient Effect of the Example 8 Transfusion Solution		
Amino Acid Transfusion Solution	Gain in Body Weight (g/7 days)	Nitrogen Balance (g/7 days)
Comparison Transfusion Solution I	8.3	0.84
Comparison Transfusion Solution II	10.0	0.95
Transfusion Solution of Example 8	13.1	1.3

TEST EXAMPLES 9 - 12

Using the transfusion solutions of Examples 9, 10, 13 and 20 and the comparison transfusion solutions set forth in Table 18 and 18a, procedures similar to those in Test Example 8 were conducted. The results are shown in Table 21.

Table 21

Nutrient Effects of the Examples 9, 10, 13 and 20 Transfusion Solution			
Test Example	Amino Acid Transfusion Solution	Gain in Body Weight (g/7 days)	Nitrogen Balance (g/7 days)
9	Transfusion of Example 9	13.5	1.5
	Comparison Transfusion Solution III	8.4	1.0
	Comparison Transfusion Solution IV	8.7	1.1
10	Transfusion Solution of Example 10	14.1	1.4
	Comparison Transfusion Solution V	9.1	0.95
	Comparison Transfusion Solution VI	9.2	1.1
11	Transfusion Solution of Example 13	14.5	1.3
	Comparison Transfusion Solution VII	9.6	1.0
	Comparison Transfusion Solution VIII	9.3	1.1
12	Transfusion Solution of Example 20	15.3	1.6
	Comparison Transfusion Solution IX	9.2	1.2
	Comparison Transfusion Solution X	8.9	1.1

The present invention relates to an amino acid composition incorporating a dipeptide of L-tyrosine which exerts an excellent nutrient effect on various diseases, and can provide, as is evident from the

foregoing examples [illegible] test examples, amino acid transfusion solutio[illegible]ntaining Tyr at high concentrations without suffering from pharmaceutical restrictions in their preparation.

In other words, since Tyr is used as its dipeptide, it was possible to formulate at a concentration suited for the purpose without suffering from the pharmaceutical restrictions.

The formulation of the invention, that is, the nutrient transfusion composition can exert excellent nutrient effects on various diseases as an amino acid transfusion solution according to the respective sick conditions or as an amino acid transfusion solution having high general-purpose utility.

The dipeptides used according to the present invention are effectively utilized to the living body.

A Fourth Embodiment

In order to solve the third problem described above, the present inventors have made various investigations on new components of transfusion solutions and, as a result, have found that the problem can be solved by using dipeptide containing an L-leucine residue. The present invention has thus been accomplished.

That is, the present invention provides, in a fourth embodiment, a nutrient transfusion composition containing essential amino acids, non-essential L-amino acids and at least one dipeptide whose molecules contain at least one L-leucine residue, which composition is characterized in that said composition contains, if said dipeptide is converted to the respective component L-amino acids, at least the respective amino acids indicated in Table 22 below in the respective compositional ranges indicated therein, that the weight ratio of the total branched chain L-amino acids to the total L-amino acids is 0.3 - 0.6, that the weight ratio of the total essential amino acids to the total non-essential amino acids is 0.9 -1.8, and that the weight ratio of Leu, Ile and Val is 1.6 - 2.4 : 0.8 - 1.2 : 0.8 - 1.2.

Table 22

Amino Acid	Compositional Range (g/100 g of total amino acids)
Ile	7.0 - 30.0
Leu	15.0 - 45.0
Lys	5.0 - 12.0
Met	2.0 - 10.0
Phe	4.0 - 10.0
Thr	4.0 - 9.0
Trp	1.0 - 5.0
Val	7.0 - 30.0
Arg	5.0 - 11.0
His	3.0 - 6.0
Gly	1.0 - 7.5
Ala	1.0 - 8.2
Cys	0 - 1.5
Asp	1.0 - 4.9
Glu	0.5 - 7.0
Pro	1.0 - 6.0
Ser	1.0 - 3.9
Tyr	0.1 - 1.5
Tan	0 - 15.0

The term "if said dipeptide is converted to the respective L-amino acids" described above means that "if an amount of said dipeptide is calculated as the amounts of the respctive L-amino acids formed when the said dipeptide is fully hydrolyzed".

The amino acid composition shown in Table 22 was determined from the view point of sitology and preparation of the nutrient transfusion composition.

All the Leu content in the transfusion composition doesn't need to be in the form of dipeptide(s) whose molecules contain at least one L-leucine residue. The dipeptide in an amount of more than about 4% of all the Leu content would suffice from the viewpoint of solublity.

Examples of the dipeptides containing at least one L-leucine residue per molecule which can be preferably used in the present invention include L-leucyl-L-isoleucine (Leu-Ile), L-leucyl-L-valine (Leu-Val), L-isoleucyl-L-leucine (Ile-Leu), L-valyl-L-leucine (Val-Leu), etc.

These peptides can be prepared by conventional peptide synthesis.

The amino acids and dipeptides in accordance with the present invention may be used in their free form or in the form of pharmacologically acceptable salts, for example, salts with metals such as sodium and potassium, salts with mineral acids such as hydrochloric acid and sulfuric acid, and salts with organic acids such as acetic acid and lactic acid. Further the L-amino acids other than those in the dipeptide form may also be used as pharmacologically acceptable N-acyl derivatives or ester derivatives or oligopeptides.

Furthermore, when an L-amino acid composition is converted into a preparation of the present invention, i.e., nutrient transfusion compositions, this preparation may be prepared in a conventional manner, using stabilizers, pH regulators, etc. ordinarily used for amino acid transfusion solutions. Its pH can be the same as those of known amino acid transfusion solutions, and may usually be in the range of about 4 to about 8.

The nutrient transfusion compositions of the present invention may also contain nutrients other than L-amino acids, such as electrolytes, trace elements, vitamins, minerals, sugars, xylitol.

They are not critical in their concentration, and can have concentrations of known amino acid transfusion solutions.

An effective dosage of the total amino acids of the present invention is 60 - 90 g/day for adults.

The preent invention is described in more detail by referring to the examples and test examples below.

EXAMPLE 21

To the amino acid composition shown in Table 23 was added 22.4 g of Leu-Ile. The mixture was dissolved in distilled water for injection by heating to make the whole volume 0.99 liter. After adjusting its pH to 6.0 - 7.0 with an aqueous acetic acid solution, the whole volume was made 1 liter. The solution was filtered through a membrane filter having a pore diameter of 0.45 µm. The filtrate was filled in a 200 ml glass bottle. After replacing the air with nitrogen gas, the bottle was tight-sealed. A nutrient solution for intravenous administeration was then prepared by steam sterilization under high pressure.

Table 23

Amounts of Amino Acids Formulated (g/l)					
Ile	0	Val	16.0	Pro	5.0
Leu	8.0	Ala	6.0	Ser	3.0
Lys	10.0	Arg	10.0	Tyr	0.5
Met	2.5	Asp	2.0	Gly	5.0
Phe	5.0	Cys	1.0	Tau	3.5
Thr	5.0	Glu	2.0		
Trp	2.5	His	5.0		

The preparation contained 12 g/l of Ile and 20 g/l of Leu if the dipeptide was converted to the respective L-amino acid components. The weight ratio of the total essential amino acids to the total non-essential amino acids (E/N) was 1.7, the ratio of the total branched chain amino acids to the total amino acids (BCAA/TAA) was 0.41, and the Ile : Leu : Val ratio was 1 : 1.7 : 1.3.

EXAMPLE 22

To the amino acid composition shown in Table 24 was added 37.3 g of Ile-Leu. Subsequently, the mixture was treated in a similar manner as in Example 21 to give a transfusion solution for intravenous administration.

Table 24

Amounts of Amino Acids Formulated (g/l)					
Ile	0	Val	20.0	Pro	9.0
Leu	20.0	Ala	12.0	Ser	3.0
Lys	12.0	Arg	14.0	Tyr	0.5
Met	7.5	Asp	2.0	Gly	13.0
Phe	12.0	Cys	1.0	Tau	7.5
Thr	13.0	Glu	2.0		
Trp	2.5	His	9.0		

The preparation contained 20 g/l of Ile and 40 g/l of Leu if the dipeptide was converted to the respective L-amino acid components. The E/N was 1.74, BCAA/TAA was 0.4, and the Ile : Leu : Val ratio was 1 : 2 : 1.

EXAMPLES 23 - 28

The amino acids and dipeptides shown in Table 25 were mixed and the mixtures were treated in a similar manner as in Example 21 to give transfusion solutions for intravenous administration.

Table 25

Amounts of Amino Acids and Dipeptides Formulated (g/l)						
Amino Acids and Dipeptides	Example No.					
	23	24	25	26	27	28
Ile	0	0	12.0	20.0	9.0	8.0
Leu	9.0	8.0	2.1	17.6	7.9	7.0
Lys	7.1	9.5	10.0	12.0	7.1	9.5
Met	4.4	3.9	2.5	7.5	4.4	3.9
Phe	7.0	7.0	5.0	12.0	7.0	7.0
Thr	7.5	5.7	5.0	13.0	7.5	5.7
Trp	1.3	2.0	2.5	2.5	1.3	2.0
Val	9.0	8.0	0	0	0	0
Ala	7.1	7.0	6.0	12.0	7.1	7.0
Arg	9.0	10.5	10.0	14.0	9.0	10.5
Asp	1.0	1.0	2.0	2.0	1.0	1.0
Cys	0	1.0	1.0	1.0	0	1.0
Glu	0.5	1.0	2.0	2.0	0.5	1.0
His	5.0	5.0	5.0	9.0	5.0	5.0
Pro	5.0	5.0	5.0	9.0	5.0	5.0
Ser	1.7	3.0	3.0	3.0	1.7	3.0
Tyr	0.4	0.5	0.5	0.5	0.4	0.5
Gly	7.0	5.9	5.0	13.0	7.0	5.9
Tau	0	0	3.5	7.5	0	0
Leu-Ile	6.8	0	0	0	0	0
Ile-Leu	0	14.9	0	0	0	0
Leu-Val	0	0	0	39.3	17.7	0
Val-Leu	0	0	31.5	0	0	15.7
E/N	1.72	1.51	1.70	1.74	1.72	1.51
BCAA/TAA	0.36	0.32	0.41	0.40	0.36	0.32
Ile:Leu:Val	1:2:1	1:2:1	1:1.7:1.3	1:2:1	1:2:1	1:2:1

TEST EXAMPLE 13

Using SD strain male rats weighing 170 - 180 g, a silicone rubber catheter was held in the right upper great vein under anesthetized condition, through which a transfusion solution was given for a week under the intravenous hyperalimentation control (total calorie: 332 Kcal/Kg/day, nitrogen: 1.83 gN/Kg/day). The nutrient transfusion solutions given had different amino acid compositions but glucose, electrolytes, vitamins and trace elements were identical. The amino acid transfusion solutions tested were those transfusion solutions shown in Examples 21 - 23 and 25 - 27, and, as comparative transfusion solutions, transfusion solutions A and B having compositions shown in Table 26 below were used.

Table 26

Amino Acids	Comparative Transfusion Solutions (g/l)	
	A	B
Ile	5.6	8.5
Leu	12.5	13.5
Lys	8.8	8.0
Met	3.5	3.9
Phe	9.4	7.7
Thr	6.5	4.8
Trp	1.3	1.6
Val	4.5	9.0
Ala	6.2	8.6
Arg	7.9	11.1
Asp	3.8	0.5
Cys	1.0	1.0
Glu	6.5	0.5
His	6.0	4.7
Pro	3.3	6.4
Ser	2.2	4.2
Tyr	0.35	0.5
Gly	10.7	5.5

The results are shown in Table 27. The amino acid transfusion solutions of the present invention showed excellent effects with respect to body weight increase and nitrogen balance of the tested animals, as compared to the comparative transfusion solutions.

Table 27

Amino Acid Transfusion Solutions	Gain in Body Weight (g/7 days)	Nitrogen Balance (mg N/day)
Example 21	10.0	101.2
Example 22	11.0	110.0
Example 23	10.5	101.5
Example 25	11.2	111.5
Example 26	10.3	100.0
Example 27	11.0	110.5
Comparative Solution A	5.5	85.5
Comparative Solution B	6.2	98.0

As is evident from the foregoing, especially from the examples and test example, the present invention is directed to amino acid compositions which can exhibit excellent nutrient effects in various diseases and can provide highly dense amino acid transfusion solutions without any preparatory restrictions. In other words, since the branched chain amino acids are used in the form of water soluble dipeptides, compositions

containing the branched chain amino acid components in a high formulation proportion can be provided to be suited for the respective intended purposes.

The nutrient transfusion solutions of the present invention can exhibit excellent nutrient effects in various diseases, as amino acid transfusion solutions for respective diseases or for general purpose.

The dipeptide in accordance with the present invention is effectively utilized in the living body.

A Fifth Embodiment

In order to solve th fourth problem described above, the present inventors have made investigations and as a result, have found that branched chain L-amino acid compositions which contain dipeptide(s) of BCAA are provided for amino acid transfusion solution. That is, according to the present invention, the problem in preparations described above can be solved by replacing a part or the whole of Leu, Ile and/or Val with dipeptide(s) whose molecules contain at least one branched chain L-amino acid residue, for example, L-leucyl-L-isoleucine (Leu-Ile), L-isoleucyl-L-leucine (Ile-Leu), L-leucyl-L-valine (Leu-Val), L-valyl-L-leucine (Val-Leu), L-isoleucyl-L-valine (Ile-Val) and L-valyl-L-isoleucine (Val-Ile). Thus, amino acid transfusion solutions for intravenous administration which contain the branched chain L-amino acids (BCAA) at a high concentration in a ratio suited for the intended purpose and have an excellent ratio of Leu, Ile and Val formulated can be prepared with the use of the BCAA compositions of the present invention. The present invention has thus been accomplished on the basis of these findings.

That is, the present invention is to provide, in a fifth embodiment, a branched chain L-amino acid composition containing at least one dipeptide whose molecules contain at least one branched chain L-amino acid residue for amino acid transfusion solutions, which composition is characterized in that the concentration of Leu has been adjusted to 20 - 100 g/l in the L-amino acid components including the respective component L-amino acids if said dipeptide is calculated as the respective component L-amino acids.

It is preferred that when the dipeptide is calculated as L-amino acids in a BCAA composition containing at least one dipeptide whose molecules contain at least one branched chain L-amino acid residue for amino acid transfusion solutions, at least the amino acids indicated in Table 28 below are contained in the compositional ranges indicated therein and the weight ratio of Leu, Ile and Val is in the range of 1.6 - 2.4 : 0.8 - 1.2 : 0.8 - 1.2 from the sitological point of view.

Table 28

Amino Acid	Compositional Range (g/l)
Leu	20.0 - 100.0
Ile	10.0 - 50.0
Val	10.0 - 50.0

The term "when the dipeptide is calculated as L-amino acids" described above means that "when an amount of the dipeptide is calculated as the amounts of the respective L-amino acids formed when the said dipeptide is fully hydrolyzed".

The amino acid composjtion shown in Table 28 is determined from the preparatory and sitological point of view.

Examples of dipeptides containing at least one branched chain L-amino acid residue which can be used in the present invention include Leu-Ile, Ile-Leu, Leu-Val, Val-Leu, Ile-Val, Val-Ile, as has been mentioned above.

In a BCAA composition of the present invention, the ratio of the BCAA in the free state and the BCAA in the dipeptide(s) form is 0 - 100 : 4 - 300.

The composition of the present invention cannot be used as an amino acid transfusion solution as it is. However, as will be shown below, amino acid transfusion solutions suitable for particular morbid conditions can readily be prepared by mixing the composition of the present invention with other amino acid compositions in an appropriate ratio.

Desired amino acid transfusion solutions can be prepared conventionally in a manner similar to known amino acid transfusion solutions except a composition of the present invention is used. Any pH value can be taken but preferred is between 4.5 and 8.0 from the physiological point of view.

Furthermore, nutrient substances such as sugars, vitamins, minerals, etc. may also be incorporated utilizing known techniques. Even when reducing sugars are formulated in the amino acid transfusion compositions, it is difficult to cause the Maillard reaction and in this sense, the compositions are advantageous.

The present invention will be described in more detail by referring to the examples and preparation examples below.

EXAMPLE 29

The branched chain amino acids and dipeptides containing the branched chain amino acid residues shown in Table 29 below were dissolved in distilled water for injection by heating to make the whole volume 0.99 liter. After adjusting its pH to 6.0 to 7.0 with an aqueous acetic acid solution, the whole volume was made 1 liter. The solution was filtered through a membrane filter having a pore diameter of 0.45 µm. The filtrate was filled in a 200 ml glass bottle. After replacing the air with nitrogen gas, the bottle was tight-sealed. This was sterilized with steam under high pressure to prepare a BCAA composition, which was supposed to be used in preparing amino acid transfusion solutions.

The composition of this example contained 30.0 g/l of Ile, 50.0 g/l of Leu and 25.0 g/l of Val.

Table 29

Amino Acid and Dipeptide	Amount Used (g/l)
Ile	10.0
Leu	10.0
Val	7.1
Leu-Ile	37.3
Leu-Val	35.1

In Examples 30 - 44, BCAA compositions to be used for amino acid transfusion solutions were prepared in a conventional manner using dipeptides containing branched chain L-amino acid residues and/or branched chain L-amino acids indicated in Tables 30 - 44, respctively.

EXAMPLE 30

Table 30

Amino Acid and Dipeptide	Amount Used (g/l)
Ile	5.0
Leu	10.0
Val	12.1
Ile-Leu	37.3
Val-Leu	35.1

The composition of this example contained 25.0 g/l of Ile, 50.0 g/l of Leu and 30.0 g/l of Val.

EXAMPLE 31

Table 31

Amino Acid and Dipeptide	Amount Used (g/l)
Ile	5.0
Leu	10.0
Val	7.1
Leu-Ile	37.3
Val-Leu	35.1

The composition of this example contained 25.0 g/l of Ile, 50.0 g/l of Leu and 25.0 g/l of Val.

EXAMPLE 32

Table 32

Amino Acid and Dipeptide	Amount Used (g/l)
Ile	10.0
Leu	10.0
Val	12.1
Ile-Leu	74.5
Leu-Val	35.1

The composition of this example contained 50.0 g/l of Ile, 70.0 g/l of Leu and 30.0 g/l of Val.

EXAMPLE 33

Table 33

Amino Acid and Dipeptide	Amount Used (g/l)
Ile	10.0
Leu	20.0
Val	20.0
Leu-Ile	37.3

The composition of this example contained 30.0 g/l of Ile, 40.0 g/l of Leu and 20.0 g/l of Val.

EXAMPLE 34

Table 34

Amino Acid and Dipeptide	Amount Used (g/l)
Leu	20.0
Val	25.0
Leu-Ile	46.6

The composition of this example contained 25.0 g/l of Ile, 45.0 g/l of Leu and 25.0 g/l of Val.

EXAMPLE 35

Table 35

Amino Acid and Dipeptide	Amount Used (g/l)
Val	2.1
Ile-Leu	37.3
Leu-Val	35.1

The composition of this example contained 20.0 g/l of Ile, 40.0 g/l of Leu and 20.0 g/l of Val.

EXAMPLE 36

Table 36

Amino Acid and Dipeptide	Amount Used (g/l)
Val	0.1
Leu-Ile	27.9
Val-Leu	35.1

The composition of this example contained 15.0 g/l of Ile, 35.0 g/l of Leu and 18.0 g/l of Val.

EXAMPLE 37

Table 37

Amino Acid and Dipeptide	Amount Used (g/l)
Leu	15.0
Val	15.0
Ile-Leu	27.9

The composition of this example contained 15.0 g/l of Ile, 30.0 g/l of Leu and 15.0 g/l of Val.

EXAMPLE 38

Table 38

Amino Acid and Dipeptide	Amount Used (g/l)
Leu	10.0
Val	10.0
Ile-Leu	18.6

The composition of this example contained 10.0 g/l of Ile, 20.0 g/l of Leu and 10.0 g/l of Val.

EXAMPLE 39

Table 39

Amino Acid and Dipeptide	Amount Used (g/l)
Leu	20.0
Val	15.5
Leu-Ile	37.3
Ile-Val	8.8

The composition of this example contained 25.0 g/l of Ile, 40.0 g/l of Leu and 20.0 g/l of Val.

EXAMPLE 40

Table 40

Amino Acid and Dipeptide	Amount Used (g/l)
Leu	20.0
Val	1.1
Val-Ile	17.6

The composition of this example contained 10.0 g/l of Ile, 20.0 g/l of Leu and 10.0 g/l of Val.

EXAMPLE 41

Table 41

Amino Acid and Dipeptide	Amount Used (g/l)
Leu	20.0
Val	1.6
Ile-Val	26.3

The composition of this example contained 15.0 g/l of Ile, 20.0 g/l of Leu and 15.0 g/l of Val.

EXAMPLE 42

Table 42

Amino Acid and Dipeptide	Amount Used (g/l)
Ile	10.0
Leu	10.0
Val	12.1
Leu-Ile	74.5
Val-Leu	35.1

The composition of this example contained 50.0 g/l of Ile, 70.0 g/l of Leu and 30.0 g/l of Val.

EXAMPLE 43

Table 43

Amino Acid and Dipeptide	Amount Used (g/l)
Leu-Ile	37.3
Leu-Val	35.1

The composition of this example contained 20.0 g/l of Ile, 40.0 g/l of Leu and 17.9 g/l of Val.

EXAMPLE 44

Table 44

Amino Acid and Dipeptide	Amount Used (g/l)
Leu-Ile	74.5
Leu-Val	70.2

The composition of this example contained 40.0 g/l of Ile, 80.0 g/l of Leu and 35.8 g/l of Val.

PREPARATION EXAMPLES 1 - 5

Portions of the BCAA composition obtained in Example 31 were mixed with a commercially available amino acid transfusion solution in various ratios in a conventional manner. Thus, amino acid transfusion solutions 1 - 5 were prepared.

The compositions of the amino acids in the transfusion solutions thus prepared are shown in Table 45.

Table 45

Composition of Amino Acids after Mixing					
Preparation Example No.	1	2	3	4	5
Mixing Ratio	0.5:1	1:1	0.1:1	0.1:1	0.1:1
Ile	11.8	15.0	7.1	11.5	10.5
Leu	24.2	30.7	15.4	19.3	16.3
Lys	8.1	6.1	10.9	13.8	6.5
Met	2.3	1.7	3.1	13.4	4.0
Phe	6.1	4.6	8.2	13.4	6.4
Thr	4.2	3.2	5.7	6.1	6.8
Trp	0.85	0.63	1.1	3.0	1.2
Val	11.1	14.5	6.2	12.1	15.0
Ala	4.0	3.0	5.5	6.7	6.5
Arg	5.1	3.9	7.0	-	8.2
Asp	2.5	1.9	3.3	-	0.91
Cys	0.65	0.49	0.88	-	-
Glu	4.2	3.2	5.7	-	0.45
His	3.9	2.9	5.3	-	4.5
Pro	2.1	1.6	2.9	-	4.5
Ser	1.4	1.1	1.9	-	1.5
Tyr	0.22	0.17	0.31	-	0.36
Gly	7.0	5.3	9.4	-	6.4

Preparations Nos. 1, 2 and 5 in the table above were obtained by mixing the BCAA composition with a commercially available amino acid transfusion solution in ratios of 0.5 : 1, 1 : 1 and 0.1 : 1, in which preparations the content of branched chain L-amino acids was relatively high and the glycine content was relatively suppressed low since glycine tends to cause hyperammonemia. These preparations are suitably administered to patients in the post-operative stage or patients without any abnormality in amino acid metabolism.

Preparation No. 3 described above was obtained by mixing the BCAA composition with the commercially available amino acid transfusion solution in a ratio of 0.1 : 1, in which preparation branched chain amino acids metabolized in organs other than liver were contained in large quantities. The preparation can improve nutritious conditions of patients with hepatic disorder.

Preparation No. 4 described above was obtained by mixing the BCAA composition with the same amino acid transfusion solution in a ratio of 0.1 : 1, in which preparation the content of non-essential L-amino acids was reduced so as to re-use blood urea and ammonia for synthesis of L-amino acids. The preparation is suited for administration to patients with renal disorder.

Thus, it is understood that by appropriately changing the mixing ratio as described above, amino acid transfusion solutions having desired compositions can readily be obtained by using BCAA compositions of the present invention.

As is evident especially from the foregoing examples and preparation examples, the BCAA composition of the present invention contains branched chain L-amino acids in a high concentration in a suitable ratio and is useful as a premixing preparation for preparing amino acid transfusion solutions for respective morbid conditions which are required to administer highly dense branched chain L-amino acids. In other words, if a conventional amino acid transfusion solution is mixed with a BCAA composition of the present invention in an appropriate ratio, then amino acid transfusion solutions can readily be prepared which solutions are suited for respective specific diseases.

According to the present invention, since branched chain L-amino acids are in the form of dipeptides, compositions for amino acid transfusion solutions can be provided in a ratio suited for the intended purposes, without any preparatory restrictions. The composition of the present invention is useful as a composition which can be formulated in amino acid transfusion solutions used for respective morbid conditions.

The dipeptides in accordance with the present invention are effectively utilized in the living body.

Claims

1. An amino acid transfusion solution or an amino acid mixture which gives an amino acid transfusion solution when dissolved in water in which solution or mixture at least one of L-tryptophan, L-tyrosine, L-Leucine, L-Isoleucine and L-Valine is partly or substantially contained in the form of oligopeptide(s) whose molecules contain at least one residue of said L-amino acids.

2. A nutrient transfusion composition containing essential L-amino acids characterized in that substantially all of the L-tryptophan is present in the form of dipeptide(s) and/or tripeptide(s) having at least one L-tryptophan residue and that it contains no stabilizers.

3. An amino acid nutrient transfusion composition containing essential amino acids, non-essential L-amino acids and at least one dipeptide containing at least one L-tyrosine residue, characterized in that at least the respective amino acids indicated in Table A are present in the respective ranges indicated when said dipeptide is calculated as the respective component L-amino acids, that the weight ratio of L-tyrosine to L-phenylalanine (L-tyrosine/L-phenylalanine) is 0.1 or more and that the concentration of L-tyrosine is 0.6 g/l or more.

Table A

Amino Acid	Composition Range (g/100 g of total Amino Acids)
L-Isoleucine	5.0 - 20.0
L-Leucine	5.0 - 20.0
L-Lysine	3.0 - 15.0
L-Methionine	1.0 - 10.0
L-Phenylalanine	1.0 - 10.0
L-Threonine	2.0 - 12.0
L-Tryptophane	0.25 - 5.0
L-Valine	5.0 - 20.0
L-Alanine	2.0 - 15.0
L-Arginine	2.0 - 15.0
L-Aspartic acid	0 - 4.0
L-Cysteine	0 - 2.0
L-Glutamic Acid	0 - 8.0
L-Histidine	0 - 10.0
L-Proline	0 - 10.0
L-Serine	0 - 8.0
L-Tyrosine	0.5 - 10.0
Glycine	3.0 - 15.0
L-Ornithine	0 - 5.0
Taurine	0 - 15.0

4. A nutrient transfusion composition containing essential amino acids, non-essential L-amino acids and at least one dipeptide whose molecules contain at least one L-leucine residue, characterized in that said composition contains at least the respective amino acids indicated in Table B in the respective compositional ranges indicated therein if said dipeptide is converted to the respective component L-amino acids, that the weight ratio of the total branched chain L-amino acids to the total L-amino acids is 0.3 - 0.6, that the weight ratio of the total essential amino acids to the total non-essential amino acids is 0.9 - 1.8, and that the weight ratio of L-leucine, L-isoleucine and L-valine is 1.6 2.4 : 0.8 - 1.2 : 0.8 - 1.2.

Table B

Amino Acid	Composition Range (g/100 g of total Amino Acids)
L-Isoleucine	7.0 - 30.0
L-Leucine	15.0 - 45.0
L-Lysine	5.0 - 12.0
L-Methionine	2.0 - 10.0
L-Phenylalanine	4.0 - 10.0
L-Threonine	4.0 - 9.0
L-Tryptophane	1.0 - 5.0
L-Valine	7.0 - 30.0
L-Arginine	5.0 - 11.0
L-Histidine	3.0 - 6.0
Glycine	1.0 - 7.5
L-Alanine	1.0 - 8.2
L-Cysteine	0 - 1.5
L-Aspartic Acid	1.0 - 4.9
L-Glutamic Acid	0.5 - 7.0
L-Proline	1.0 - 6.0
L-Serine	1.0 - 3.9
L-Tyrosine	0.1 - 1.5
Taurine	0 - 15.0

5. A branched chain L-amino acid composition for amino acid transfusion solutions containing at least one dipeptide whose molecules contain at least one branched chain L-amino acid residue characterized in that the concentration of L-leucine is adjusted to 20 - 100 g/l in the L-amino acid components including the respective component L-amino acids if said dipeptide is calculated as the respective component L-amino acids.

Amended claims in accordance with Rule 86(2) EPC.

1. An amino acid infusion solution or an amino acid mixture which gives an amino acid infusion solution when dissolved in water in which solution or mixture at least one of L-tryptophan, L-tyrosine, L-Leucine, L-Isoleucine and L-Valine is partly or substantially contained in the form of oligopeptide(s) whose molecules contain at least one residue of said L-amino acids.

-2. A nutrient infusion composition containing essential L-amino acids characterized in that substantially all of the L-tryptophan is present in the form of dipeptide(s) and/or tripeptide(s) having at least one L-tryptophan residue and that it contains no stabilizers.

3. An amino acid nutrient infusion composition containing essential amino acids, non-essential L-amino acids and at least one dipeptide containing at least one L-tyrosine residue, characterized in that at least the respective amino acids indicated in Table A are present in the respective ranges indicated when said dipeptide is calculated as the respective component L-amino acids, that the weight ratio of L-tyrosine to L-phenylalanine

4. A nutrient infusion composition containing essential amino acids, non-essential L-amino acids and at least one dipeptide whose molecules contain at least one L-leucine residue, characterized in that said composition contains at least the respective amino acids indicated in Table B in the respective ranges of composition indicated therein if said dipeptide is converted to the respective component L-amino acids, that the weight ratio of the total branched chain L-amino acids to the total L-amino acids is 0.3 - 0.6, that the weight ratio of the total essential amino acids to the total non-essential amino acids is 0.9 - 1.8, and that the weight ratio of L-leucine, L-isoleucine and L-valine is 1.6 2.4 : 0.8 - 1.2 : 0.8 - 1.2.

Table B

Amino Acid	Composition Range (g/100 g of total Amino Acids)
L-Isoleucine	7.0 - 30.0
L-Leucine	15.0 - 45.0
L-Lysine	5.0 - 12.0
L-Methionine	2.0 - 10.0
L-Phenylalanine	4.0 - 10.0
L-Threonine	4.0 - 9.0
L-Tryptophane	1.0 - 5.0
L-Valine	7.0 - 30.0
L-Arginine	5.0 - 11.0
L-Histidine	3.0 - 6.0
Glycine	1.0 - 7.5
L-Alanine	1.0 - 8.2
L-Cysteine	0 - 1.5
L-Aspartic Acid	1.0 - 4.9
L-Glutamic Acid	0.5 - 7.0
L-Proline	1.0 - 6.0
L-Serine	1.0 - 3.9
L-Tyrosine	0.1 - 1.5
Taurine	0 - 15.0

5. A branched chain L-amino acid composition for amino acid infusion solutions containing at least one dipeptide whose molecules contain at least one branched chain L-amino acid residue characterized in that the concentration of L-leucine is adjusted to 20 - 100 g/l in the L-amino acid components including the respective component L-amino acids if said dipeptide is calculated as the respective component L-amino acids.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 89 11 1321

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X	EP-A-0 182 356 (PFRIMMER & CO.) * page 9, table 3; claims 1-4,6-10 *	1,4	A 23 L 1/305
D,X	PATENT ABSTRACTS OF JAPAN vol. 5, no. 54 (C-50)(726), 15 April 1981; & JP - A - 56 8312 (OOTSUKA SEIYAKU KOUJIYOU K.K.) 28.01.1981	1,2	
X	GB-A-2 071 670 (SIAMAK A. ADIBI) * claims 1-5 *	1	
D,A	PATENT ABSTRACTS OF JAPAN vol. 11, no. 381 (C-464)(2828), 12 December 1987; & JP - A - 62 151156 (AJINOMOTO CO. INC.) 06.07.87	4	
A	PATENT ABSTRACTS OF JAPAN vol. 10, no. 144 (C-349)(2201), 27 May 1986; & JP - A - 61 5096 (TAKEDA YAKUHIN KOGYO K.K.) 10.01.1986	1	
X	PATENT ABSTRACTS OF JAPAN vol. 10, no. 103 (C-340)(2160), 18 April 1986; & JP - A - 60 233099 (ASAHI KASEI KOGYO K.K.) 19.11.1985	1,4	TECHNICAL FIELDS SEARCHED (Int. Cl.4) A 23 L 1/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	01-09-1989	SCHULTZE D

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document